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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,867	10/25/2000	Mary E. Brunkow	240083.501D6	2612

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/696,867	BRUNKOW ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *35,40-42,44,46 and 47*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *03/09/04*.

10. ☐ Other: _____

JEFFREY FREDMAN
PRIMARY EXAMINER

Continuation of 2. NOTE: Newly proposed claim limitation "operably linked to **a promoter** effective for the expression an Fkh polypeptide, wherein proliferation of T lymphocytes that are obtained from the transgenic mouse expressing the Fkh transgene is reduced when compared to proliferation of T cells obtained from a scurfy mouse" would require additional search and or consideration under 35 USC 112(1) regarding enablement issues.

Continuation of 5. does NOT place the application in condition for allowance because: Claim 35, 40, 42, 44 and 46-47 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30kb fragment of normal genomic DNA, including ~7kb coding region of Fkh^{sf} gene as well as ~20kb of upstream flanking sequence and ~4kb of down stream sequences that contain a sequence encoding mouse Fkh^{sf} protein wherein the expression of exogenous Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the scurfy mouse, does not reasonably provide enablement for any transgenic mouse, whose cells express an Fkh^{sf} transgene encoding mouse Fkh^{sf} (SEQ ID NO:1) or human Fkh^{sf} (SEQ ID NO:3), wherein the expression of the Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal.

The applicant argues that applicants fully enabled the claimed invention directed in pertinent part to a transgenic mouse whose cells express an Fkh transgene comprising a nucleic acid molecule that comprises a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2. The applicant argues that the invention as claimed and described in the specification is not directed to a transgenic scurfy mouse but is instead directed to a transgenic mouse that is derived by microinjecting normal genomic DNA that contains wild type Fkh coding sequence into normal mouse one-cell embryos. The applicant argues that the "these animals do not express the mutant polypeptide that contains the *sf* mutation, a two base insertion in the Fkh^{sf} coding region (see page 32) but express normal wild type Fkh polypeptide (see page 33)". The applicant argues that the in view of the state of the art and in view of enabling guidance provided in the working examples a skilled artisan knows how to make and use the claimed transgenic mice. The applicant argues that the specification as filed enables making and using transgenic mice that express the human **Fkh^{sf}** polypeptide.

However, applicant's argument are found NOT persuasive because Example-1, pages 32-33 of the specification as filed only discloses generation of a transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30kb fragment of normal genomic DNA, including ~7kb coding region of Fkh^{sf} gene as well as ~20kb of upstream flanking sequence and ~4kb of down stream sequences that contain a sequence encoding mouse Fkh^{sf} protein wherein the expression of exogenous Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the scurfy mouse (see page 33 sec b, lines 10-27 specifically). At best the specification as filed teaches that the addition of the normal Fkh gene can overcome the defect found in **scurfy mice**, confirming that the mutation in the Fkh gene is the cause of Scurfy disease (see spec. page 33 lines 25-27). The specification as filed fails to disclose any transgenic mouse with normal Fkh^{sf} gene, which also encodes a transgene comprising a promoter operably linked to the a nucleotide sequence encoding Fkh^{sf} polypeptide and have reduced proliferation of T lymphocytes when compared to proliferation of T cells obtained from a scurfy mouse. It should be noted that any transgenic mouse having a normal Fkh^{sf} gene would have phenotype of a wild-type mouse. The office has clearly provided the evidence that making a transgenic mouse wherein the transgene has not been defined by its structure and function and the resultant phenotype is considered highly unpredictable, since the phenotype of an animal is determined by a complex interaction of genetics and environment. The individual

gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene (see pages 4-6 of earlier office action mailed 12/09/03). Making a transgenic mouse wherein the transgene has not been identified by its structural and functional limitation is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.